CARDIAC GLYCOSIDES

Steroids

Chemistry of Steroid Compounds

Steroids constitute a natural product class of compounds that is widely distributed throughout nature. The diversity of biologic activities of steroids includes the development and control of the reproductive tract in humans (estradiol, progesterone, testosterone) the molting of insects (ecdysone), and the induction of sexual reproduction in aquatic fungi (antheridiol). In addition, steroids contribute to a wide range of therapeutic applications, such as cardiotonics (digitoxin), vitamin D precursors (ergosterol), oral contraceptive agents (semisynthetic estrogens and progestins), anti-inflammatory agents (corticosteroids), and anabolic agents (androgens).

A steroid is any compound that contains a cyclopentanoperhydrophenanthrene nucleus (1-17 carbon atoms in Fig.12.1). The chemical nomenclature of steroids is based on this fundamental carbo-cycle with adjacent side-chain carbon atoms. Steroids are numbered and rings are lettered as indicated in the structural formula for cholesterol (Fig. 12.1). If one or more of the carbon atoms shown in the structure of cholesterol is not present, the numbering of the remainder is undisturbed.

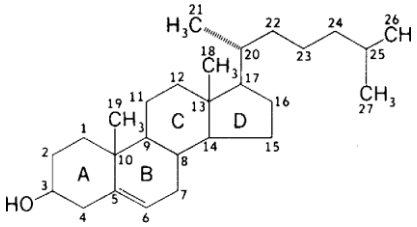


Figure 12.1. Cholesterol

When the rings of a steroid are denoted as projections onto the plane of the paper an atom or group attached to a ring is termed α if it lies below the plane of the paper or β if it lies above the plane of the paper. In formulas, bonds to atoms or groups attached in α configuration are shown as broken lines and bonds to atoms or groups attached in β configuration are shown as solid lines.

The use of a steroid stem name implies that atoms or groups attached at the ring-junction positions 8, 9, 10, 13, and 14 are oriented as shown in Fig.12.2 (8β, 9α, 10β, 13β, 14α) and a carbon chain β attached to position 17 is assumed to be β-oriented. In most steroids, rings B and C and rings C and D are fused *trans*, whereas rings A and B may be fused either *cis* or *trans*.

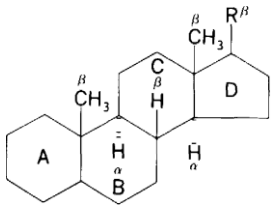


Figure 12.2. Orientation of steroid substituents

Biosynthesis of Steroids

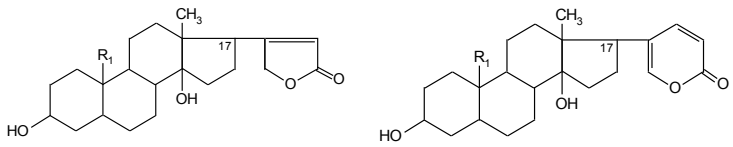
Steroids are formed biosynthetically from isopentenyl pyrophosphate (active isoprene) and involve the same sequence of reactions as does terpenoid biosynthesis. In fact, the triterpenoid squalene is an intermediate in steroid biosynthesis. Most knowledge of the biosynthesis of steroids has been derived from studies of cholesterol production. Although this compound is not necessarily a direct precursor of all other steroids, its formation may be considered as a general mechanism of steroid biosynthesis. The familiar acetate → mevalonate → isopentenyl pyrophosphate → squalene → cholesterol pathway.

Cardiac Glycosides

Chemical Structure and Classification of Cardiac Glycosides

Cardiac glycosides constitute a group of closely related natural products with highly specific and powerful action on cardiac muscles (cardiotonic). They act on the heart by direct, as well as, indirect mechanism to enhance the force and velocity of contraction. They are toxic at high doses, and with therapeutic action at smaller doses. They showed effects on the tone, excitability and contractility of the cardiac muscle and diuretic activity. In addition, they slow the rate of atrioventricular conduction. Higher doses cause toxic and sometimes lethal effects. Plants and preparations containing cardiac glycosides have long been used both as poisons and drugs in herbal medicine since ancient times.

Cardiac glycosides are steroid derivatives, characterized by the presence of a lactone ring attached to C-17β-position and a sugar moiety at the 3β- position. The steroid aglycones or genins are of 2 types: a cardenolide or a bufadienolide. The more prevalent in nature are the cardenolides, which are C_{23} steroids that have as a 17β-side chain an α/β-unsaturated 5-membered lactone ring (Fig.12.3). The bufadienolides are C_{24} homologs of the cardenolides and carry a doubly unsaturated 6-membered lactone ring at the 17-position (Fig.12.3).



Cardenolide Bufadienolide

Figure 12.3. Aglycone types of cardiac glycosides

The bufadienolides derive their name from the generic name for the toad, *Bufo* (the prototype compound bufalin was isolated from the skin of toads).

An unusual aspect of the chemistry of both cardenolides and bufadienolides is that the C/D ring junction has the *cis*-configuration. To obtain optimum cardiac activity, the aglycone should possess an α/β-unsaturated lactone ring that is attached at the 17-position of the steroid nucleus and the A/B and C/D ring junctions should have the *cis*-configuration.

Table 12.1.

Comparison between cardenolides and bufadenolides

	Cardenolides (butadienolides)	**Bufadienolides** (pentadienolide or scilladienolides)
Structure	5-membered (4 carbons) lactone ring	6-membered (5 carbons) lactone ring
Distribution	*Digitalis, Strophanthus*	*Squill, Hellebore*
UV absorbance	220 nm	300 nm
Tests for lactone ring	Kedde's, Tollen, Legal and Raymond's	
	- Positive	- Negative

Characteristic Features

1. An unsaturated lactone ring attached to steroid nucleus at C 17 with β-configuration.
2. A tertiary β-hydroxy group at C-14.
3. An axially oriented hydroxy group at C-3 to which is attached the sugar residue.
4. The *cis* fusion of the ring C/D and in most cases also of the rings A/B.
5. Methyl groups at C-10 and C-13.
6. The methyl group at C-19 may be replaced by a CHO or CH_2OH group (e.g. Strophanthus).
7. Additional hydroxy groups may be present at C-, C-2, C-5, C-l1, C-12 and C-16.

Table 12.2.

Some typical genins have the following groups in the positions indicated

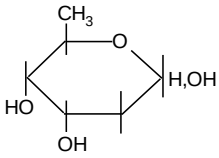
	C-1	C-3	C-5	C-10	C-11	C-12	C-14	C-16
Digitoxigenin	-	OH	H	CH_3	-	-	OH	-
Gitoxigenin	-	OH	H	CH_3	-	-	OH	OH
Digoxigenin		OH	H	CH_3	-	OH	OH	-
Strophanthidin	-	OH	OH	CHO	-	-	OH	-
Ouabagenin	OH	OH	OH	CH_2OH	OH	-	OH	-
Scillaridin A	-	OH	H	CH_3	-	-	OH	-

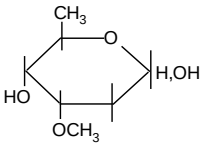
Sugar component: Although the fundamental pharmacological activity of these glycosides resides in the genin, the activity is considerably modified by the sugar moiety. The sugars when combined with the aglycones increase both the potency and toxicity of the active principle. In addition, the sugars affect certain physical properties of this chemical combination, such as solubility in water and diffusion through semipermeable membranes and consequently the rate of absorption and transportation of the compounds. The genin may be attached to one, two, three, or four monosaccharide molecules which have the chain structure of di-, tri- or tetrasaccharides. Thus from a single genin one may have a series of tetra-, tri-, di-, or mono-glycosides. Under suitable conditions of hydrolysis, e.g. by specific enzymes, the sugar units may be progressively removed from the sugar chain from the end furthest from the genin. Some of the sugar units found in cardiac glycosides are normal ones such as the hexose, glucose and the methyl pentose rhamnose; others are desoxy sugars, containing less than the normal amount of oxygen, which have so far not been found in nature except in cardiac glycosides. Among these sugars which are sometimes referred to as the "rare" sugars may be mentioned antiarose (deoxyglucose); digitalose (a methyl ether of antiarose). The preceding table shows examples of important cardiac glycosides arranged to show their genin and sugar components. Abbreviations used for the sugars are: Gl— glucose, Rh— rhamnose, Dl— digitalose, Dx— digitoxose, Th— thevetose and Cy— cymarose. The abbreviation (Ac) indicates that the sugar is acetylated and the presence of such groups generally tends towards diminishing the cardiac activity.

It may be noted also, that digitoxose and cymarose are 2-desoxy sugars which give certain reactions on desoxysugar (e.g. Keller-Killiani test). A number of other 6-desoxy hexoses also occur in various cardenolide glycosides. Some of the sugars occurring in cardioactive glycosides are of the L-configuration. Generally, the L-sugars (e.g. L-rhamnose) in these glycosides are of the α-configuration while the D-sugars have the β-

configuration.

The number and kinds of sugars in a given glycoside largely determine the solubility of the glycoside in water and other polar solvents. The steroidal aglycones are, in most cases, practically water-insoluble, but chloroform soluble.





D-Digitoxose *D-Acetyldigitoxose*

Distribution of Cardiac Glycosides

Cardiac glycosides are mainly distributed in following families: Apocynaceae *(Strophanthus),* Scrophulariaceae *(Digitalis),* Liliaceae *(Urginea),* Ranunculaceae *(Adonis).*

They are found in variety of plants over a broad geographic area. The best source of cardiac glycosides is *Digitalis purpurea* (purple foxglove) found in Europe and Asia. They may found in seeds *(Strophanthus),* leaves *(Digitalis),* fruits *(Acokanthera),* bulbs *(Urginea),* roots *(Apocynum)* or herbs *(Adonis),*

Physic and Chemical Properties of Cardiac Glycosides

Cardiac glycosides are bitter in taste, crystalline and odorless. With the exception of oubain, they are hydrophobic compounds slightly soluble in water but, freely soluble in alcohol. Treatment of cardiac glycosides with dilute acids result in hydrolysis of glycosidic bond. More drastic conditions lead to elimination of C-l4 hydroxy group with the formation of 14,15-anhydro derivatives. In the presence of alkali, depending on the conditions, the following reactions could take place isomerization of the lactone ring from the unstable β-oriented to the stable α-orinted position and an addition reaction of the C-14 hydroxy group on the lactone ring to give an iso-cardenolide.

Acid Hydrolysis

The glycosidic linkages in these glycosides are cleaved by acid hydrolysis breaking them down to sugars and aglycones. There is not any given method of acid hydrolysis suitable both for the isolation and study of the intact aglycone and at the same time suitable for the isolation and study of the intact sugar or sugars of a glycoside or group of glycosides.

Certain conditions of acid hydrolysis, in addition to breaking the glycosidic linkages, may destroy the structure of the sugars while certain other conditions of acid hydrolysis may damage the structure of the aglycone.

In a glycoside in which there are two or more monosaccharide units in the molecule, it is practically impossible to cleave off one sugar unit at a time by acid hydrolysis. In such cases when stepwise hydrolysis of one glycosidic linkage at a time is desired, it is usually achieved by the use of specific enzymes.

Hydrolytic cleavage of the glycosidic linkages involving "rare sugars", without destroying the sugar molecules, may be achieved by acid hydrolysis under mild conditions in specially devised media. For the separation of the sugar or sugars from the aglycone, after hydrolysis, the reaction mixture may be neutralized with sodium carbonate solution, and then extracted with chloroform. The steroidal aglycones are soluble in chloroform while the sugars are insoluble but water soluble. Also the cardiac glycosides are partly hydrolyzed by the acidity of the stomach but not fast enough to warrant concern in therapy.

Enzyme Hydrolysis

In many of the cardioactive plants, enzymes are present which split the glycosides into a free sugar and a secondary glycoside which contain less sugar. If special precautions are not taken during the drying and storage of many cardiac drugs, the enzyme split off sugar, usually the terminal glucose, from the original glycosides to form less complex compounds. Methods for inactivating such enzymes in the course of extraction have already been mentioned. For the isolation of the terminal glucose units in such glycosides, or for cleaving off glucose that is attached directly to the aglycone, certain specific enzymes obtained from various sources have been used for cleaving off such glucose units, without splitting off other sugars present in the same glucoside molecule.

The enzyme digilanidase removes the terminal glucose in lanatosides A and B and purpureaglycosides A and B. The enzyme strophanthobiase (obtained from the seeds of *Strophanthus courmonti)* hydrolyzes the linkage bridging the terminal glucose to cymarose in the glycoside K-strophanthin B. A glycoside from yeast is capable of hydrolyzirig the linkage between the two glucose units in the glycoside K-strophanthoside.

Reactions with Alkali

Mild alkaline hydrolysis removes the O-acetyl group (as acetic acid) from those

glycosides which contain such a group attached to one of the sugar units, (e.g. as in lanatosides A, B and C and acetyldigitoxin, etc.). Thus mild alkaline hydrolysis of acetyl digitoxin gives acetic acid and digitoxin. Similarly lanatoside A and B by the same treatment give purpurea glycosides A and B respectively.

In the presence of strong solution of caustic alkali, the lactone ring that is attached to C-17, in the aglycone of these glycosides is easily opened, whereby the salt of the aldehydic acid is formed. Once opened, however, it does not re-form to yield the original lactone (cardenolide). The carboxyl now forms a lactone with a hydroxyl located in other parts of the aglycone to yield iso-genins, which are physiologically inactive. It follows that the presence of strong alkali destroys the activity of cardiac glycosides.

Methods of Isolation and Chemical Tests of Cardiac Glycosides

It is relatively easy to obtain a crude extract of plant material containing cardioactive glycosides by extracting the material with alcohol or alcohol-water mixture. However, isolating each of these glycosides in pure crystalline form and without converting some of these glycosides into their hydrolytic products requires some of these glycosides into their hydrolytic of these cardioactive glycosides, especially the highly water soluble ones. Because of action of enzymes present in the plant materials in which these glycosides occur, those glycosides which contain terminal glucose units (e.g. lanatosides A, B, C, D and E and purpurea glycoside A and B), are liable to lose the glucose in the process of extraction, lnactivation of the enzymes by methods such as those referred to before or other methods is necessary to prevent the loss of such terminal glucose in the isolation of these glycosides. Enzymes capable of cleaving the linkages between two rare sugars or the linkages between rare sugar and aglycone are apparently absent in the plant materials in which these glycosides occur or they are not as active under the usual conditions of extraction.

The following procedures may be suggested for the isolation of a wide variety of steroidal cardioactive glycosides and the study of their aglycones and the "rare" sugars they contain, providing that the terminal glucose is not to be preserved intact, or when the glycosides in question do not contain such terminal glucose.

The fatty matter is removed from the plant material by extraction with petroleum ether. The defatted material is digested with water at 0-4°C to remove the polysaccharides. The water extract is discarded and the marc is extracted with several portions of water ethanol mixtures increasing the alcohol content progressively. The hydro-alcoholic extract is concentrated to a smaller volume by distilling it in vacuum at 50°C.

Tannins are precipitated from the concentrate with lead hydroxide, and filtered. The filtrate is treated according to the rate of solubility of the glycosides in' water as follows:

A. **For Glycosides with Relatively High Solubility in Water**:

Adjust the filtrate to pH 6. Wash successively with ether, chloroform, and chloroform ethanol mixtures and discard the washings. Into the aqueous phase containing the glycosides dissolve sodium sulfate and extract with chloroform ethanol mixtures. In case of the more polar glycosides, they are actylated or benzoylated and later the glycosides liberated by hydrolysis with $KHCO_3$. Separation of the individual glycosides is achieved by chromatography on silicagel and elution with ethyl acetate containing graded portions of methyl alcohol, increasing from 0,5 to 5 %.

B. For Glycosides with Relatively Low Solubility in Water and High Solubility in Chloroform:

The filtrate is treed from alcohol by distillation in vacuum and the aqueous solution is extracted with chloroform. The chloroform extract is washed with water, 2N HCl, 2N Na_2CO_3 and water and the washings are discarded. Separation of the individual glycosides is achieved by chromatography on silica gel and elution with chloroform and chloroform containing graded portions of methyl alcohol.

Of course, special structural characteristic in a particular glycoside or a particular group of glycosides have to be taken in consideration in devising suitable modifications of such a procedure. For example, in case of glycosides with an aldehyde function in their molecular structure (such as those with strophanthidin as the aglycone), they can be separated from other glycosides by the use of Girard's reagent which contains the hydrazide of carboxymethyl trimethyl ammonium chloride. This reagent would convert the water insoluble aldehydes (or κetones) to the corresponding water-soluble hydrazones, and the aldehyde may later be liberated from the hydrazone by hydrolysis.

Chemical Tests

Cardiac glycosides give color reactions with different reagents. These can be used for qualitative and quantitative purposes, as well as, spray reagents on TLC.

Test for Sterols

Liebermann test for sterols: This test is characteristic of aglycones of the scillarenin type (the squill glycosides) and is due to the steroid part of the molecule. The test is carried by adding one drop of concentrated sulfuric acid to a solution of the glycoside in glacial

acetic acid. A change in color occurs from red, through violet and blue to green.

Test with antimony trichloride; Both the cardenoiides and the bufadienolides (sciiladienolides) give this color reaction. When most of these cardioactive glycosides are heated with antimony trichloride and trichloracetic acid, a blue or violet color is obtained.

Test for Aglycone Moiety

Legal test: This is a test for unsaturated lactones. The test may be carried out as follows: A small quantity (a few mg) of the glycoside (except scillaren) is dissolved in a few drops of pyridine. A drop of 2 per cent sodium nitroprusside and a drop of 20 per cent sodium hydroxide solution are then added. Production of a deep red color constitutes a positive test.

Raymond test: A positive Raymond test depends on the presence of an activated methylene group (C-31 in the lactonc ring of the cardenolides). A small quantity of the glycoside is dissolved in 1 ml. of 50% ethanol, and this is followed by the addition of 0.1 ml. of a 1% solution of dinitro-benzene in ethanol (or methanol). To this solution are then added two or three drops of a 20 per cent sodium hydroxide solution. Appearance of a violet color (which then changes to blue) constitutes a positive test.

Kedde reagent: This is widely used for spraying developed chromatograms of the cardenoiides (or glycosides containing cardenolide aglycones). This reagent is essentially a modified form of the reagents used for the Raymond test. The Kedde reagent may be prepared by mixing equal volumes of a 2% solution of 3, 5-dinitrobenzoic acid in methanol and a 5-7% aqueous solution of potassium hydroxide. The cardenolides react with this reagent to give a blue or violet color, which fades in one or two hours.

Tollens test: A small quantity of the glycoside is dissolved in a few drops of pyridine. Ammoniacal silver nitrate solution is then added. Liberation of silver constitutes a positive test.

Test for Sugars

Keller-Kiliani test: The 2-desoxy sugars (or the glycosides containing 2-desoxy sugars) respond to this test. This test may not be reliable if the sugar is acetylated. The glycoside is dissolved in glacial acetic acid containing a trace of ferric chloride; concentrated sulfuric acid containing the same amount of ferric chloride is placed at the bottom of the test tube with a pipette. An intense blue color develops at the surface between the two reagents in 2-5 minutes spreading gradually into the acetic acid layer.

Xanthydrol test: This test is given by 2-desoxy sugars. When these are heated in solution of xanthydrol in glacial acetic acid containing 1% HC1, a red color is developed.

Quantitative Determination

Method adopted for determination of cardiac glycosides includes:

1. Colorimetric method
2. Fluorimetric method
3. Gravimetric method
4. Biological method (determination of LD50)
5. Immunoassay (radioimmunoassay)
6. RP-HPLC with UV or fluorometric detector

Therapeutic Effect of Cardiac Glycosides

The use of the cardiac glycosides in therapeutics stems from the ability of these compounds to increase the force of systolic contraction. An increase in contractility in the failing heart results in a more complete emptying of the ventricle and a shortening in the length of systole. Thus, the heart has more time to rest between contractions. As the myocardium recovers as a result of increased cardiac output and circulation, the heart rate is decreased through a reflex vagal effect. In addition, the improved circulation tends to improve renal secretion, which relieves the edema often associated with heart failure.

In the use of cardiac glycosides to treat congestive heart failure, the patient is given an initial loading dose of the drug in order to bring the heart under the influence of the drug. Because the amount required varies with the patient and the drug used, the preparation is given in divided doses while titrating the dose against signs of improvement. The patient is usually maintained indefinitely after the loading dose by administering a daily maintenance dose that replaces the amount of drug that is metabolized and excreted. In toxic concentrations, the glycosides may increase cardiac automaticity and lead to ectopic tachyarrhythmia. Ventricular extrasystoles are the most frequent effect. With all the glycosides, the therapeutic level appears to be approximately 50 to 60% of the toxic dose. This finding explains why dosage must be carefully determined experimentally for each patient.

Despite numerous experimental investigations, the mechanism of action of the cardiac glycosides is still not completely known; however, observations have implicated Na^+, K^+ -ATPas as the receptor enzyme. This enzyme catalyzes the active transport of Na^+ out of the cell and the subsequent transport of K^+ into the cell. Na^+, K^+ - ATPas operates in all cell membranes to maintain the unequal distribution of Na^+ and K^+ ions across the membrane. However, in the myocardium the ion exchange is rapid because it is required after each heart beat; therefore, an inhibition of Na^+, K^+ -ATPas has a greater effect on heart tissue than on other cells of the body.

When the heart beats, a wave of depolarization passes through it, changing the permeability of the cell membranes. Na^+ moves into the cell by passive diffusion and K^+ moves out. Na^+, K^+ -ATPas supplies the energy from ATP to reverse this process and to pump the Na^+ out of the cell and the K^+ into the cell against a concentration gradient.

Inhibition of Na^+, K^+-ATPase by the cardiac glycoside results in an increase in Na^+ and a decrease K^+ within the cell which, in turn, stimulates a secondary Na^+ Ca^{2+} exchange mechanism that functions to remove intracellular Na^+ with a subsequent increase in intracellular Ca^{2+}. The positive inotropic action or muscle contraction enhancement of cardiac glycosides is mediated through the increase in Ca^{2+}. Ca^{2+} interacts with troponin which then, through its action on tropomyosin, unmasks the binding sites on actin that bind myosin, allowing for the formation of the contractile protein actomyosin.

Because of the narrow therapeutic range of cardiac glycosides, knowledge of their pharmacokinetic is essential for safe therapy (therapeutic effect of digoxin: 1-2 ng/ml and toxic effect: > 2.5 ng/ml). They are very similar in their pharmacodynamic action but differ in their pharmacokinetic according to their lipophilicities. These differences include:

- Absorption after oral administration
- Plasma protein binding
- Rate of elimination
- Onset of action
- Duration of action
- Mode of excretion

Structure-Activity Relationships

The sugar moieties have no cardiac activities, but when attached to 3-OH group of the steroid they modify the activity and are of great importance for the pharmacokinetic behavior. They affect the potency of the cardiac glycosides.

Cardiac glycosides with 6-deoxy sugar are more potent than the corresponding 6-CH_2OH analogs. In oligosaccharides the potency decreases in the order: Monosaccharide >disacchardide > trisaccharide >aglycone.

Aglycone Moiety

Oxygen substitution on the steroidal nucleus affects the distribution and metabolism, the more -OH groups the more rapid onset of action and subsequent elimination from the body.

The activity of the cardiac glycosides is due to the aglycone part, in particular to the lactone ring (opening by alkali, results in loss of the activity), the cis-junction of the ring A/B and C/D and the 3-OH group.

Lactone ring. For many years, it was believed that the unsaturated lactone ring is key group for the activity, later on it was found that the lactone ring could be replaced by unsaturated ester derivatives. Saturation of the lactone ring reduces the potency 10 folds.

It was found that the β-oriented C-17 side chain is required for the activity and 17 α-cardenolides (allo-cardenolides) are inactive. Ring junction A/B and C/D. The A/B cis fused rings are more potent than A/B *trans.* It was found that cis-junction of the rings C/D is required for the cardiac activity.

C-3 and C-14 hydroxyl groups. Replacement of the C-3 and C-14 hydroxyl groups with hydrogens reduces the potency slightly.

Administration

Glycosides with long duration of action. Digitoxigenin derived glycosides are characterized by a long duration of action, e.g. digitoxin (Lanatoxin®, Digilong®, Digimerck®).

Glycosides with medium duration of action. Digoxin (Lanoxin®, Digacin®, Lanicor®) and its derivatives have intermediate pharmacokinetic properties between digitoxin and the short acting *Strophanthus* glycosides. Acetyldigoxin (Dioxanin®, Lanatilin®) is prepared from lanatoside C by removal of the terminal glucose unit by enzyme hydrolysis.

Glycosides with short duration of action. *Strophanthus* glycosides are characterized by a rapid onset and a very short duration of action, used only for intravenous therapy. Ouabain (Purostrophan®, Strodival®) and Proscillaridin (Sandoscill®, Talusin®) are used when rapid action is required, especially in acute congestive heart failure. Elimination is independent on renal function.

Digitalis purpurea glycosides.	more cumulative than those of *D. lanata*
Strophanthus glycosides (ouabain)	rapid action, and rapid elimination
Adonis, Hellbore glycosides	shorter duration, and stronger action

Doses

Initial loading dose: The dose needed to bring the heart under the influence of the drug.

Maintenance dose: The daily administered dose that replaces the amount of drug that

is metabolized and excreted.

Medicinal Plants and Raw Material Containing Cardiac Glycosides

DIGITALIS LEAVES (PURPLE FOXGLOVE LEAVES) – *DIGITALIS FOLIA*

Digitalis (Purple Foxglove) - *Digitalis purpurea* L., Fam. Scrophulariaceae**.**

Synonym(s): Foxglove, Dead Men's Bells, Dog's Finger, Fairy Fingers, Finger Rower.

Plant. The plant is a biennial with a branched tap root. In the first year it develops a leaf rosette. In the second it produces a 2 m high, erect, unbranched, gray, tomentose stem. The leaves are alternate, ovate, tapering upward and petiolate. Almost all leaves are crenate; only the highest ones are entire-margined. The flowers are carmine red with white edged spots on the inside. The flowers appear in long hanging racemes. They have 5 free, short-tipped sepals. The corolla is about 4 cm long, campanulate, bilabiate with an obtuse upper lip and an ovate tip on the lower lip. The flower is glabrous on the outside and has a white awn on the inside. There are 2 long and 2 short stamens, and 1 superior ovary. The fruit is a 2-valved, ovate, glandular, villous capsule. The plant is very poisonous; it tastes hotbitter with a slightly unpleasant odor.

The medicinal parts are the dried leaves (in powder form), the ripe dried seeds, the fresh leaves of the 1-year-old plant or the leaves of the 2-year-old plant collected at the beginning of flowering. In the past, the drug of Purple Foxglove was the raw material employed in isolating the cardiac glycosides. The rose leaves are harvested during the first period of vegetation in early autumn. The drying period is decisive for the content of cardenolide glycosides. The temperature for drying is 30° C to 50° C.

Area of distribution. *Digitalis* is indigenous to Europe. It was introduced to the east and the American continent.

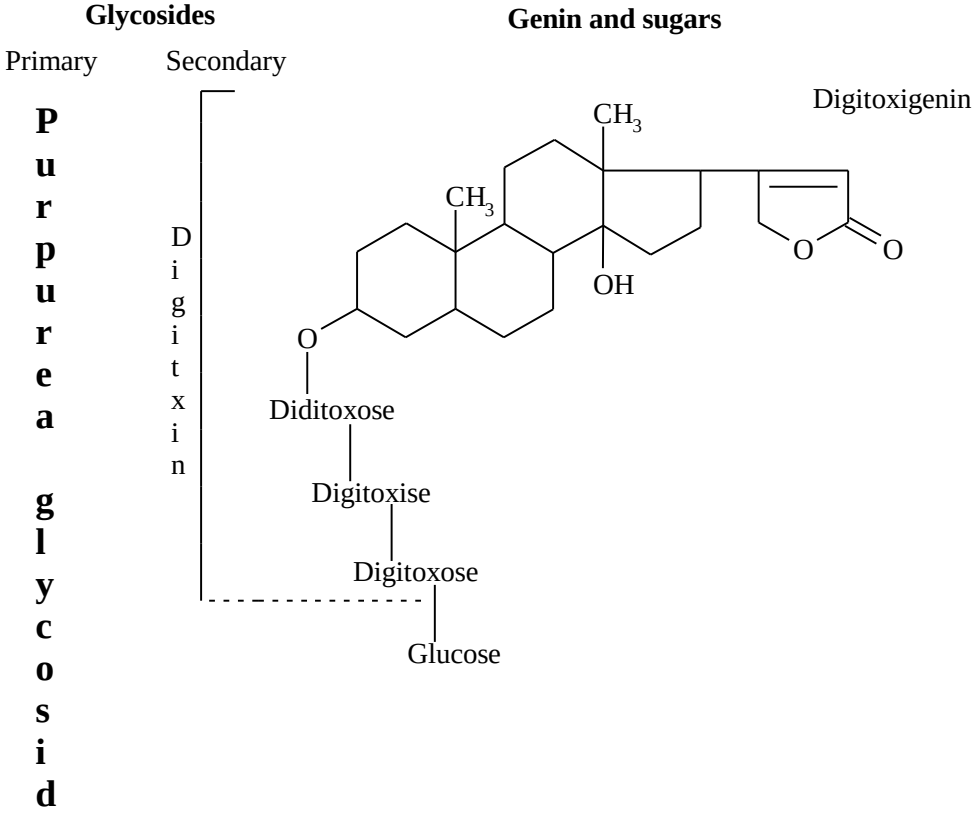
Description. Digitalis leaves are usually ovate-lanceolate to broadly ovate in shape, from petiolate to sessile and about 10-30 cm long and 4-10 cm wide. The lamina is decurrent at the base; apex is subacute. The margin is crenate or dentate. Both surfaces are hairs, particularly the lower one and a fringe of fine hairs is found on the margin. The veins are depressed on the upper

surface, but very prominent from the lower one. The main veins leave the midrib at an acute angle, afterwards branching and anastomosing repeatedly. The leaves are of a dark greyish-green colour. The drag has no marked odour, but a bitter taste.

Constituents. Cardioactive steroid glycosides (cardenolides 0.5 to 1.5%): including ones of the:

- A-sequence (aglycone digitoxigenin): purpurea glycoside A (primary glycoside), digitoxin (secondary glycoside)
- B-sequence (aglycone gitoxigenin): purpurea glycoside B (primary glycoside), gitoxin (secondary glycoside).
- E-sequence (aglycone gitaloxigenin): glucoverodoxin, glucogitaloxin, gitaloxin. Pregnane glycosides: including digipurpurin, diginin, digitalonin.

Steroid saponin: including desgalactotigonin. digitonine, purpureagitoside. Anthracene derivatives: anthraquinones.



Uses. Drug contains cardioactive cardenolide glycosides are positively inotropic, negatively chronotropic and improve the contraction power of cardiac muscle. “Digitoxin”, “Gitoxin”, “Cordigit” - cardiotonic in the treatment of congestive heart failure and disturbances of circulation.

Side effects. With overdosage, in addition to the already-mentioned symptoms, the following can also occur: **Heart:** cardiac rhythm disorders, all the way up to life threatening ventricular tachycardia, atrial tachycardia with atrioventricular block. **Central nervous system:** stupor, visual disorders, depression, confused states, hallucinations, psychoses. **Lethal dosages:** lead to

heart failure or asphyxiation.

Homeopathic Uses: *Digitalis purpurea* is used for cardiac insufficiency and migraine.

Pharmacopoeial and Other Monographs: BP 2009, Ph. Eur. 6.4.

DIGITALIS LANATA LEAF –*DIGITALIS LANATAE FOLIA*

Wooly Foxglove, Grecian Foxglove - *Digitalis lanata* Ehrh., Fam. Scrophulariaceae**.**

Plant. *Digitalis lanata* is a herbaceous biennial or perennial, upright, up to 1.2 m high. The leaves are sessile, simple, narrow-lanceolate, 15 to 35 cm long, entire and ciliate in the upper area of the shoot axis. The stem is upright, usually green, grooved-edged, usually glabrous below and long woolly-haired in the upper half. The plant has a primary root with no shoot-bearing roots. The inflorescence is long and densely flowered, with racemes facing all directions. The bracts are glandular-haired with ciliate edges. The flower structures are in fives. The sepals are fused, the calyx tubular. The petals are fused to a campanulate corolla, which is glandular-haired on, the outside, white with yellow-brown spots, 18 to 25 mm long and unevenly bilabiate. The upper lip has 4 points, and is flat and hem-like. The lower lip is almost as long as the corolla tube and is turned away from it. There are 4 stamens, often stretching out of the corolla tube. The ovaries are superior, 2-chambered, clavate, glandular-haired, gradually merging into the stigmas. The fruit is a 10 mm long septicidal, brittle capsule. The seeds are approximately 1.5 mm long and red-brown.

The leaves are the medicinal part of the plant. Woolly foxglove leaves are the dried leaves of *Digitalis lanata*. Annual cultivation begins with sowing in April; harvesting is between September and November. The roughly cut leaves are dried for 10 to 12 hours at 50° C.

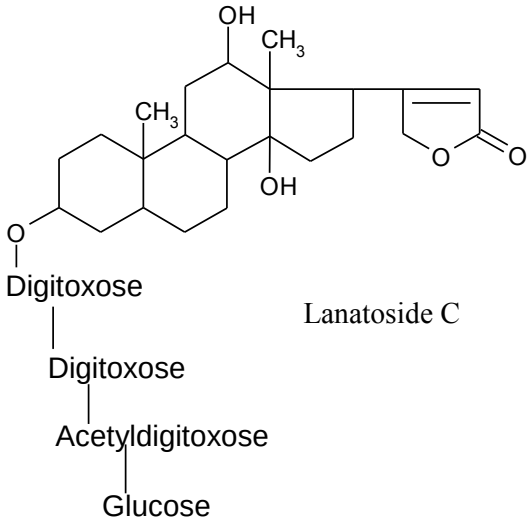
Area of distribution. The plant's habitat extends from Greece and the Balkans across the northern coast of the Black Sea to the Caucasus and the Caspian Sea.

Description. The leaves are linear-lanceolate to oblong- lanceolate in shape, sessile, slightly leather-like and up to about 30 cm long and 4 cm broad. The apex is acuminate and the veins leave the midrib at a very acute angle. The surface of leaves is naked, the colour of the upper surface is green, the lower one is light-green. The odor is weak, peculiar, the taste is bitter.

Constituents. Cardioactive steroid glycosides (cardenolides 0.5 to 1.5%) of the following series, including:

A-series (aglycone digitoxigenin): including lanatoside A (0.05 to 0.25%) glucodigifucoside (0.01 to 0.15%), glucoevatromonoside (0.02 to 0.05%), digitoxin, α and β-acetyldigoxin.

B-series (aglycone gitoxigenin): lanatoside B (0.01 to 0.15%), glucogitoroside (0.02 to 0.12%).



Lanatoside C

Uses. The cardioactive cardenolide glycosides contained in the drug are positively inotropic and negatively chronotropic. *Digitalis lanata* is known to be highly resorbent when administered orally. It produces rapid results and wide-ranging effects; has strong diuretic properties; is quickly abating; and demonstrates good tolerability. *Digitalis lanata* has three times the physiological effect of *Digitalis purpurea* and is preferred for its fast-acting effect. Despite these qualities, the drug is now obsolete and has been replaced by pure cardenolide glycosides. «Digoxin», «Celanid», «Lanatoside», «Lanatoside C», «Acetyldigitoxin» - cardiotonic in the treatment of congestive heart failure and disturbances of circulation.

Side effects. With overdosage, in addition to the symptoms above, the following can also occur: **Heart:** Cardiac rhythm disorders as serious as life-threatening ventricular tachycardias and atrial tachycardias with atrioventricular block. **Central nervous system:** Dizziness, vision disorders, depressions, states of confusion, hallucinations and psychoses. **Lethal dosages** (for humans, 2 to 3 g of the drug) initially lead to signs of nausea, vomiting and diarrhea caused by irritation of the gastrointestinal tract. Slowed pulse, extrasystoles and conduction disturbances result from resorption. These are followed by ventricular fibrillation and later death from cardiac arrest.

CONVALLARIA (THE LILY-OF-THE-VALLEY) HERB - *CONVALLARIAE HERBA*

CONVALLARIA LEAF – *CONVALLARIAE FOLIA*

CONVALLARIA FLOWER - *CONVALLARIAE FLORES*

Lily-of-the-valley (Convallaria) - *Convallaria majalis* L., Fam. Liliaceae.

Synonym(s): May Lily, May Bells, Our Lady's Tears, Jacob's Ladder, Ladder-to-Heaven, Muguet.

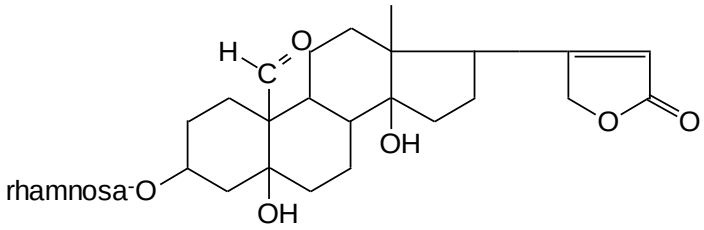
Plant. The 15 to 20 cm high plant has 2 to 3 leaves at the tip of the runner-like, branched rhizome. The leaves are elliptoid and acute. They taper to a long, sharp petiole at the base, which is clasped by a membranous sheath. The flowers are in racemes nodding to one side, usually with a triangular penduncle. The tips are hemispheric, campanulate, 6-petalled with ovoid revolute tips. The perigone is white or pink. The stamens are attached to the base of the perigone. The fruit is a bright red, globular berry with 2 blue seeds. The plant is autosterile.

The medicinal parts are the dried flower tips and the dried inflorescence, the Lily-of-the-Valley herb, the flowering aerial parts and the whole, fresh, flowering plant. Lily-of-the-Valley herb consists of the dried, above-ground parts of *Convallaria majalis* (or closely related species) ottected during the flowering season. The harvested parts of the plant must be dried quickly at maximum temperature of 60°C. Lilly-of-the-Valley is easily confused with Polygonatum odoratum.

Area of distribution. The plant is native to Europe and has been introduced into the U.S. and northern Asia.

Description. Leaves with long sheaths, separate or conjugate, oval or oblong-elliptical in shape; acuminate, entire, glabrous on both sides, with arching venation, green, petioles often yellowish. The leaf is 10-20 cm long, 3-8 cm wide. Flower scapes are naked, light green triangular or half rounded in crossection, terminating in a unilateral loose raceme. Flowers with a simple perianth on bent flower stems, emerging from the axils of short, filmy, lanceolate bracts. The corolla-like perianth is bell-shaped, 6 stamens on short filaments fixed at base of the perianth. Odour is weak, faint.

Constituents. Cardioactive steroid glycosides (cardenolides): varying according to geographical source, chief glycoside convallatoxin (western and northwestern Europe), convalloside (northern and eastern Europe), or convallatoxin + convallatoxol (central Europe).



Convallotoxin

Uses. Only older studies are available, which indicate the *Convallaria* glycosides are qualitatively similar to digitoxin and strophanthin. The studies show Lily-of-the-Valley to have the following effects: **Cardiac:** The power and speed of cardiac muscle contraction is increased and there is a reduced relaxation time. The beat frequency is slowed, stimulation transfer is delayed and the ability of the chamber muscles to be stimulated is increased (positively

inotropic, negatively chronotropic, negatively dromotropic and positively bathmotropic effect). **Renal:** In animal tests, the effect was natriuretic and diuretic. **Venous:** In animal tests, Lily-of-the-Valley demonstrated a dose-dependent, veno-constrictive effect. Tincture, "Corglycon" - cardiotonic in the treatment of congestive heart failure and disturbances of circulation. "Convaflavin" – cholagogic.

Side effects. For symptoms of an acute poisoning see *Digitalis* folium. The dangers of poisoning are relatively low with oral application, due to the poor absorbability of the glycosides.

Pharmacopoeial and Other Monographs: BHP 1996, USSR Ph. 11 ed.

FRESH GRAY WALLFLOWER HERB - *ERYSIMI CANESCENTIS RECENTIS HERBA*

Gray Wallflower - *Erysimum canescens* Roth and *Erysimum diffusum* Ehrh. Fam. Brassicaceae.

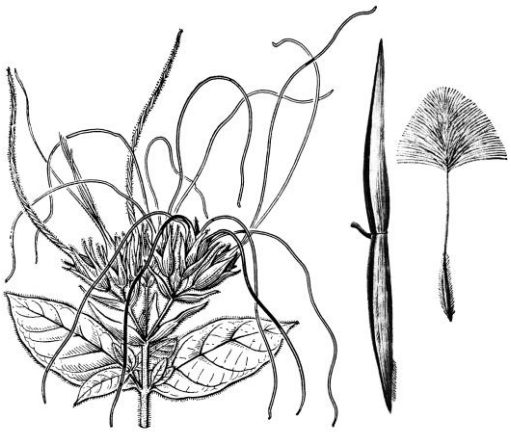
Plant. A Gray Wallflower is a herbaceous biennial or perennial upright that grows up to 1.2 m high. The leaves are alternate. The lower ones are petiolate, 1 to 8 mm wide, gray-haired, narrow, linear-lanceolate, entire or dentate; the middle and upper ones are sessile. The stem is edged, covered in jointed hairs and branched in larger plants. The root is thin, spindle-shaped and branched. The flowers are in densely flowered racemes. The 4 sepals are upright and gray-haired, the 4 petals yellow, long-petiolate, pubescent on the lower surface and 8 to 14 mm long. There are 2 short and 4 long stamens; the ovary is superior with 4 fused carpels. The fruit is a 3.5 to 8 cm long, approximately 1 mm wide, 4-sided, appressed pubescent, dehiscent pod that opens on 2 sides. The seeds are elongate with a diameter of approximately 1 to 1.5 mm.

The medicinal part is the plant's radish. The gray-leaved wild radish is collected during the flowering season of the two-year-old plants of *Erysimum diffusum* and dried after harvesting at a maximum temperature of 40° C.

Area of distribution. The plant is indigenous to the Commonwealth of Independent States and Hungary.

Constituents. Cardioactive steroid glycosides (cardenolids, 1 to 3%): chief component erysimoside (primary glycoside, aglycone K-strophanthidin 0.6%), helveticoside {secondary glycoside), canescine, cheirotoxin, erycanoside.

Uses. The drug contains cardioactive glycosides of the cardenolide type with K-strophantidin as the aglycone. It is accordingly positively inotropic and negatively chronotropic in its effect. «Cardiovalen», «Erysimin» - cardiotonic, diuretic, sedative.



STROPHANTHUS SEED – *STROPHANTHI SEMINA*

Strophanthus species – *Strophanthus Kombe* Oliv., *Strophanthus hispidus* DC, *Strophanthus gratus* (Hook.) Franch, Fam. Apocynaceae.

Plant. The plants are climbing lianes, occasionally erect shrubs, subshrubs or trees. They contain milky latex. The eaves are opposite, ovate to elliptical, short-petioled, simple, entire-margined and usually coriaceous. The flowers are in terminal or lateral panicles with few flowers or in richly blossomed, umbelliferous panicles. Their parts are in fives. They are white or yellowish, radially symmetrical and sometimes fragrant. The calyx has 5 elliptical-lanceolate to obovate sepals and a short tube with a campanulately splayed upper part, which has 10 scales on the margin. The anthers are acute with a partly tailed middle section. The ovary is 2-valved, semi-inferior and has numerous ovules. The fruit has 1 to 2 follicles, which are oblong, 8 to 58 cm long, splayed or horizontal on one level. The greenish-brown seeds are 8 to 25 mm long, fusiform and often flattened. The seeds have an awn-like appendage and a long tuft of hair at the base, which eventually drops off.

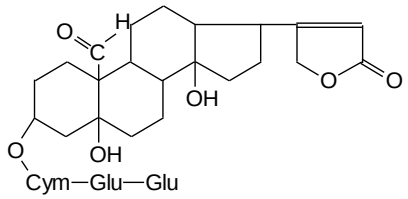
The medicinal parts are the ripe seeds, which have been freed from their appendages and dried. The plants are poisonous.

Area of distribution. *Strophanthus* is indigenous to tropical Africa.

Description. The seeds are lanceolate or linear-lanceolate in shape, somewhat flattened, 12 to 18 mm long, 3-5 mm broad. The testa is densely covered with grayish-green or fawny silky hairs, which are directed towards the acuminate apex. On the ventral surface a small ridge, the raphe, runs from a point near the centre of the seed to its apex.

Constituents. *Strophanthus gratus* seeds - cardioactive steroid glycosides (cardenolides, 3-8%): chief glycoside strophanthin-G (ouabain, over 80%), further including acolongifloroside K, strogoside, among others.

Strophanthus Kombe seeds - **c**ardioactive steroid glycosides: cardenolides, 4-4.5%, the mixture known as Strophanthin-K chief glycoside K-strophanthoside (60-80%), erysimoside (15-25%), strophoside, (10-15%), saponins (0.2%), fatty oil (35%) are also found in Strophanthus seeds.



K-strophanthoside

Uses. The active agent, Strophanthin-G, is a cardioactive glycoside that has actions similar to digitalis, but is milder. No clinical test results are available. The drug is poorly absorbed by the gastrointestinal tract. Strophanthus is used for arteriosclerosis, cardiac insufficiency, gastrocardial symptoms, hypertension and neurodystonia. «Strphanthin-K», «Strophanthin -G», «Strophanthidin acetate» - cardiotonic**.** Homeopathic Uses: Strophanthus is used for cardiac insufficiency and anxiety.

ADONIS HERB (SPRING PHEASANT'S EYE HERB) – *ADONIDIS VERNALIS HERBA*

Spring Pheasant's eye - *Adonis vernalis* L., Fam. Ranunculaceae.

Plant. The plant is 10 to 40 cm high with a sturdy, black-brown rhizome. The stem is erect, undivided, covered with scales at the base, vertically grooved and succulent. There are few branches. The leaves have many slits and a curved, glabrous or sparsely haired tip. The middle leaves are half-clasping. The erect, solitary, terminal flower is 4 to 7 cm in diameter and the 5 broad-ovate, downy sepals are half as long as the petals. The 10 to 20 petals are narrow, wedge-shaped, simple or finely serrated at the tip. They are 20 to 40 mm long and lemon-yellow, splayed, glossy, reddish on the outside or greenish-tinged. There are numerous stamens and carpels. The small fruit forms a globose capitulum. The fruit is tomentose, wrinkled, laterally veined and keeled widi a sideways-facing, hook-shaped beak. The fruit are arranged on the spindle-shaped, oblong receptacle.

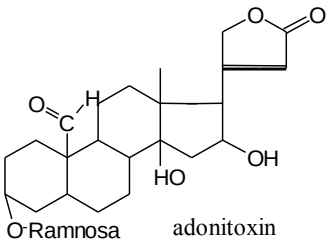
The medicinal part is derived from the aerial parts of the herb, which are collected during the flowering season and dried at the temperature of about 60^{o}C.

Area of distribution. This Siberian-east European plant is found in the north as far as the central Urals and southwest Sweden. In central Europe, it is limited to the basins of the Weichsel and the Oder as far as the Main and Rhine.

Description. Raw material is represented by densely-leaved shoots about 35 cm in length, with flowers or without them, sometimes with flower-buds or fruits of various stage of development. The leaves are wide-ovate in shape, palmate-sected in 5 linear segments; two lower of them are

shorter than others. Flowers are arranged at the apex of the stem an branches; they have 10-20 oblong-elliptical goldish-yellow petals. Calyx is green, downy; it has 5-8 calyx lobes, ovate in shape. Fruit is oval in shape, consisting of numerous, fine greenish nutlets. The odour is weak, characteristic, the taste is bitter.

Constituents. The herb contains cardiac glycosides (cardenolids): adonitoxin, cymarin, K-strophanthin-β. Flavonoids: including vitexin and luteolin: saponins, tannins, carotines, ascorbic acid are also found.



Adonitoxin

Uses. The preparations of *Adonis* is used for mild impairment of heart functions, especially when accompanied by nervous symptoms. «Adonisid», tablet «Adonis-bromine» - cardiotonic, sedative. Homeopathic Uses: Preparations of *Adonis* are used for cardiac insufficiency.

OLEANDER LEAF –OLEANDRI FOLIA

Oleander – *Nerium oleander* L., Fam. Apocynaceae.

Synonym(s)**:** Rose Laurel

Plant. The evergreen plant can be tree or shrub-like. The trunks are up to 4 m high. The leaves are 6 to 12 by 1.2 to 2 cm, linear-lanceolate, sharp-edged, coriaceous, dark green. The corolla is 4 to 7 mm in diameter, usually pink to red but sometimes white. The petals are thickly covered in glands. The tube is 2 cm long as are the obtuse and patent lobes. The anther appendages are long, pubescent and twisted. The follicles are 8 to 16 cm by 0.5 to 1 cm, erect and reddish-brown.

Area of distribution. *Nerium oleander* grows mainly in the Mediterranean region but also in parts of Asia. It is cultivated in Europe.

Constituents. Cardiac steroids (cardenolide): chief components are 16-acetyl neogistonin, adynerin, 5-α-adynerin, gentiobiosyladynerin, delta 16-dehydroadynerin, digitoxigenin oleandroside, gentibioosyl-odoroside A, gentiobiosyl-oleandrin, glucosylleandrin, oleandrigenin glucoside, kaneroside, neriaside, nerigoside.

Uses. Oleander is positively inotropic and negatively chronotropic. The cardenolide glycosides of the drug are qualitatively digitoxin-like in their action, but generally weaker, probably due to

the lower rate of absorption. Folk medicine uses of Oleander leaf include diseases and functional disorders of the heart, as well as skin diseases. Previous internal application for myocardial insufficiency, decompensated hypertonia and cardiac insufficiency is no longer common. No health hazards are known in conjunction with the proper administration of designated therapeutic dosages. Side effects can include, particularly in the case of overdosages, nausea, vomiting, diarrhea, headache, stupor and cardiac arrhythmias.

SQUILL BULB –*SCILLAE BULBUS*

Squill (Urginea maritima) – *Scilla maritima* L., Fam. Liliaceae.

Synonym(s)**:** Scilla, Sea Onion, Urginea, Urginea maritima (L.) Baker, Urginea scilla Steinh., White Squill.

Plant. The flowering stem is erect and 50 to 150 cm high. It is often washed purple and glabrous. The flowers, which often number 100, are arranged in richly flowered, dense racemes up to 60 cm long. The bracts are membranous and pointed. They are shorter than the pedicles and drop early. The pedicles are up to 3 cm long, thin and smooth. The flowers are white, radial and star-shaped. The ovary is ovate to oblong triangular. The capsule is ovate to oblong, 3-valved, obtuse or almost pointed. Each chamber has 1 to 4 seeds, which are elongate, flattened, smooth, glossy and winged. The plant is a perennial bulb plant. The bulbs are pear-shaped, about 15 to 30 cm in diameter. They are rarely sold whole commercially, as they tend to start growing. The fracture is short, tough and flexible.

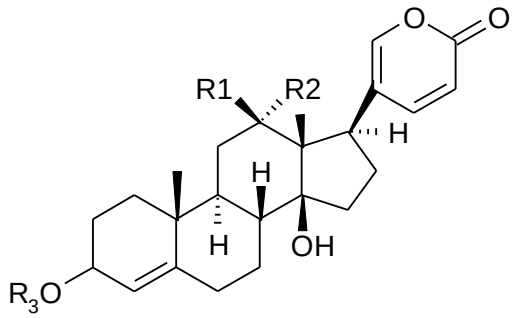
The medicinal parts come from the bulbs of the white latex variety collected after flowering and the fresh, fleshy bulb scales of the white variety and of the red variety.

Area of distribution. Indigenous to the Mediterranean and is cultivated there too. Squill consists of the sliced, dried, fleshy middle scales of the onion of the white variety of *Urginea maritima*, harvested during the flowering season. It is collected mostly from uncultivated regions.

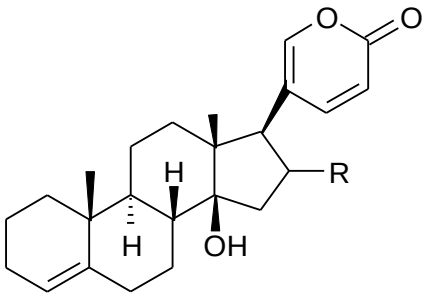
Description. Transverse slices, about 5-8 mm thick, occurring as straight or curved triangular pieces about 5-50 mm long and 3-8 mm wide at mid-point, tapering towards each end, yellowish white, texture horny, somewhat translucent, breaking with an almost glassy fracture when quite dry, but readily absorbing moisture when exposed to the air and becoming tough and flexible; transversely cut surface showing a single row of prominent, vascular bundles near the concave edge and numerous smaller bundles scattered throughout the mesophyll. Odorless or almost odorless.

Constituents. Cardioactive steroid glycosides: (bufadienolides, 1-3%): chief components glucoscillarene A, proscillaridin A, scillarene A; including among others, scillicyanoside,

scilliglaucoside. Flavonoids: apigenin, dihydroquercetin, isovitexin, iso-orientin, luteolin, orientin, quercetin, taxifolin and vitexin. Other constituents: stigmasterol, tannin, volatile and fixed oils, mucilage.



R_1=H, R_2=H, R3=H, scillarenin
R_1=H, R_2=H, R3=Rha, proscillaridin A
R_1=H, R_2=H, R_3=Glu-Rha, scillaren A
R_1=H, R_2=H, R_3=Glu-Glu-Rha, glucoscillaren A
R_1=OH, R_2=H, R_3=Rha, scilliphaeoside
R_1=OH, R_2=H, R_3=Glu-Rha, glucoscilliphaeoside



R=H, scilliglaucoside
R=$OCOCH_3$, scillicyanoside

Uses. The aglycone components of the cardiac glycoside constituents possess digitalis-like cardiotonic properties. However, the squill aglycones are poorly absorbed from the gastrointestinal tract and are less potent than digitalis cardiac glycosides. Expectorant, emetic and diuretic properties have been documented for white squill. Squill is reported to induce vomiting by both a central action and local gastric irritation. Subemetic or near-emetic doses of squill appear to exhibit an expectorant effect, causing an increase in the flow of gastric secretions. Antiseborrheic properties have been documented for methanol extracts of red squill which have been employed as hair tonics for the treatment of chronic seborrhea and dandruff.

Pharmacopoeial and Other Monographs: BHC 1992, BHP 1996, BP 2009, Complete German Commission E, Martindale 35th edition.

HELLEBORE RHIZOME AND ROOT - *HELLEBORI RHIZOMATA CUM RADICIBUS*

Green Hellebore- *Helleborus viridis* L., Fam. Ranunculaceae**.**

Plant. This herbaceous perennial grows upright, up to 40 cm high. There are 2 basal, long-petioled leaves; the lamina is divided like a foot into 7 to 13 sections that are narrow-lanceolate, serrate and dark green. The stem is upright, branching higher up and leafless to that point. The cauline leaves are similar to the basal ones but sessile and smaller. The rhizome is usually branched. There are 2 to 3 flowers with a diameter of 4 to 7 cm and 5 ovate, grass-green, broad flower bracts. The petals are in the form of petaloid

honey glands, and there are numerous stamens. The ovary is superior with the carpels only fused at the base. The fruit is a 25 to 28 mm long follicle with beak. The seeds have a narrow longitudinal strip with a ring at the end.

Area of distribution. The various species of Hellebore grow mainly in mountainous regions of Europe and North America. The plant is most commonly found in the Alps; Helleborus viridis is found growing as far north as northwest France.

Constituents. Chief component hellebrin, including deglucohellebrin. Alkaloids of unknown structure: celliamine, sprintillamine, sprintilline The steroid saponin mixture helleborin is severely toxic and irritating to mucous membranes. It exhibits digitalis-like effects through the cardioactive glycosides it contains (hellebrin).

Uses. The drug is obsolete today because the risks of use are considered too high, given that efficacy for previously accepted indications has not yet been proven. Previous uses in folk medicine included nausea, constipation and worm infestation. Root preparations were used also for heart failure and as a diuretic. *Helleborus viridis* was employed as a laxative according to Hager (around 1930) and was important in homeopathic medicine.

The drug is not to be administered in allopathic medicine. No risks are known in connection with the administration of homeopathic dosages of the drug. Homeopathic Uses: *Helleborus viridis* is used for diarrhea.

Side effects. The mucous membrane-irritating effect of the saponins appears to play the largest role in poisonings with the drug, resulting in scratchiness in mouth and throat, salivation, nausea, vomiting, diarrhea, dizziness, shortness of breath, and possible convulsions and asphyxiation. The ingestion of very large dosages leads to disorders of cardiac function (cardiac arrhythmias).